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10/544,123	08/02/2005	Michel Schneider	BR-033 PUS 01	7493

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BRACCO RESEARCH USA INC.
305- COLLEGE ROAD EAST
PRINCETON, NJ 08540

EXAMINER	
SCHLIENTZ, LEAH H	
ART UNIT	PAPER NUMBER
1618	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/544,123	SCHNEIDER ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 41-99* is/are pending in the application.

4a) Of the above claim(s) *74 and 75* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,41-73 and 76-99* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/3/2009, 8/28/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement of Receipt

Applicant's Response, filed 8/3/2009, in reply to the Office Action mailed 4/28/2009, is acknowledged and has been entered. Claims 1 and 66 have been amended. Claims 1 and 41-99 are pending, of which claims 73-75 are withdrawn from consideration at this time as being drawn to a non-elected invention. Claims 1, 41-72 and 76-99 are readable upon the elected invention and are examined herein on the merits for patentability.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on 8/3/2009 and 8/28/2007 have been considered by the examiner and signed copies are provided herewith.

Response to Arguments

Any rejection not reiterated herein has been withdrawn as being overcome by amendment. Applicant's arguments have been fully considered, but are not persuasive for reasons set forth hereinbelow.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 41-73 and 76-99 are rejected under 35 U.S.C. 103(a) as being unpatentable over Unger (WO 98/04074), for reasons set forth in the previous Office Acdtion.

Applicant argues on pages 15-16 of the Response that Unger fails to teach or suggest lyophilization of a lipid-containing aqueous-organic emulsion. With respect to Example 9, Applicant asserts that Unger does not contain any lyophilization step, as required by the claimed method, and that the final product obtained following the procedure disclosed in Example 9 is in fact an aqueous-organic mixture containing lipid particles. Applicant argues that there is no motivation for the skilled person to add an additional lyophilization step, as this mixture is in fact the final desired product to be used in the method disclosed by Unger (according to e.g. page 13, lines 6-24 of Unger).

With respect to Example 10, Applicant argues that the procedure of Example 9 is followed except that (i) l-bromoperfluorobutane is used in place of the perfluorohexane of Example 9 and added before the heating and sonication step (whereas in Example 9 perfluorohexane is added after heating); (ii) the lipid aggregates are lyophilized; and (iii) the aggregates are stored under air or insoluble gas. Applicant asserts that Example 10 is a prophetic example and that the accuracy in the drafting of the prophetic examples in

the Unger reference is rather poor; and that by following the teaching of prophetic Example 10, the skilled person would not arrive at lyophilizing a lipid-containing aqueous-organic emulsion. As a matter of fact, 1-bromoperfluorobutane has a boiling point of 43°C, and that heating treatment would inevitably result in the evaporation of the added 1-bromoperfluorobutane, having a boiling point lower than the temperature of the heated mixture. The result is that the subsequent lyophilization step foreseen is performed on an aqueous suspension of the lipids and not on an aqueous/organic emulsion of the lipids, as required instead by the present invention.

This is not found to be persuasive. Regarding Example 9 not teaching a lyophilization step, Unger at page 50, lines 29+ specifically states that as those skilled in the art will recognize, any of the lipid, protein, polymer, etc. and/or vesicle compositions may be lyophilized for storage, and reconstituted, for example with aqueous medium (such as sterile water, phosphate buffered solution, or aqueous saline solution), with the aid of vigorous agitation. To prevent agglutination or fusion of the lipids as a result of lyophilization, it may be useful to include additives which prevent such fusion or agglutination from occuring, such as sorbitol, mannitol, sodium chloride, etc. Lyophilized preparations generally have the advantage of greater shelf life. Accordingly, Unger provides adequate motivation for including a lyoprotectant and performing lyophilization (i.e. to improve shelf life upon storage). With respect to Example 10, the broader teaching of Unger teaches that a variety of fluorocarbons may be employed, including higher boiling perfluorocarbons, such as in Example 9, and

when viewed in combination with Example 9, it is evident that perfluorocarbon need not be evaporated in all formulations.

Double Patenting

Claims 1, 41-73 and 76-99 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10-13 of copending Application No. 11/202,008 for reasons set forth in the previous Office Action.

Claims 1, 41-73 and 76-99 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 35-39 of copending Application No. 10/584,327 for reasons set forth in the previous Office Action.

Claims 1, 41-73 and 76-99 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 38-42 of copending Application No. 10/584,382 for reasons set forth in the previous Office Action.

Claims 1, 41-73 and 76-99 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-35 of copending Application No. 11/641,289 for reasons set forth in the previous Office Action.

Claims 1, 41-73 and 76-99 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-35 of

copending Application No. 11/660,188 for reasons set forth in the previous Office Action.

Claim Objections

Claims 45 and 61 are objected to because of the following informalities: the claims lack punctuation at the end of the sentence. Appropriate correction is required.

New Grounds for Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 41-73, 76-99 are rejected under 35 U.S.C. 103(a) as being unpatentable over Linder (WO 94/01140) in view of Unger (WO 98/04074) and Dugstad *et al.* (US 6,221,337).

Linder discloses microbubble compositions reconstitutable in aqueous systems that are useful as echographic contrast agents prepared by lyophilizing aqueous emulsions which contain parenterally acceptable emulsifiers, apolar liquids and lipid-soluble or water-insoluble builders. These lyophilisates are characterized by a remarkable storage stability and when reconstituted with water they produce microbubble-containing echographic contrast agents characterized by microbubbles having a very small diameter and a surprisingly high stability (abstract). Emulsifiers are primarily phospholipids and poloxamers contained in the aqueous emulsions in an amount of 0.5 to 10 percent (see machine-generated english translation, page 1, lines 35+). As phospholipids phosphatidyl glycerols, phosphatidylinositol, phosphatidylethanolamine and phosphatidylserine come into question. Preferably lysoform are negatively charged phospholipids (translation page 2, lines 1-6). As non-polar liquids, for example, petroleum ether and fluorinated or chlorinated hydrocarbons are disclosed, preferably with boiling point from 30 to 65. Non-polar liquids are present in the aqueous emulsions in quanitty of 1 to 50 percent (translation page 2, lines 7-11). Conventional excipients such as saccharides are included, such as mannitol, sucrose, etc (translation page 2, lines 16-20). Particularly preferred particle size is up to 0.5 micron. See example 1, comprising dissolving 30.0 g poloxamer 188 and 54.0 g mannitol in 800 ml water for injections. 30.0 g and 20.0 g cholesterol, phosphatidylglycerol were dissolved in 100.0 g of the petroleum ether. The aqueous phase is added with vigorous stirring into the lipid phase. It fills with water for injection to

1 liter. It is then homogenized until a particle size is achieved by less than 4 microns. The resulting emulsion is filled into vials and lyophilized (translation page 2, lines 36+).

Linder does not specifically teach at least that the amphiphilic material of the emulsifying composition comprises more than 50% by weight of phospholipid.

Unger discloses in Example 9 lipid aggregates including hydration of dry lipids by heating and stirring (70 % DMPC / 20% DMPA / 10% DMPE-PEG5000), heating at 45-50 C, and sonication. Perfluorohexane was added to the mixture and the mixture was agitated. Particle size is from 0.5 to 10 microns to an entire population of particles under 2 microns. Micrometer filtration is disclosed. Unger also teaches that it is advantageous to include a lyoprotectant such as sorbitol, mannitol, etc. (page 51), and that lyophilization has benefits such as extended shelf life.

Dugstad discloses microbubble dispersions stabilized by phospholipids predominantly comprising molecules which individually have an overall net charge exhibit advantageous stability, rendering them useful as efficacious contrast agents. An improved process for preparing microbubble-containing contrast agents is also disclosed, this comprising lyophilising an aqueous dispersion of gas microbubbles stabilized by one or more membrane-forming lipids to yield a dried product which may be reconstituted in an injectable carrier liquid to generate a microbubble-containing contrast agent (abstract). According to one embodiment of the invention, a contrast agent for use in the diagnostic studies comprises a suspension of injectable aqueous carrier liquid of gas microbubbles stabilized by phospholipid-containing amphiphilic material characterized in that said amphiphilic material consists essentially of

phospholipid predominantly comprising molecules with net charges. Desirably at least 75% of the phospholipid material bears a net overal charge. Phosphatidylserines represent particularly preferred phospholipids, including dipalmitoylphosphatidylserine, etc. (column 4, lines 9-67). Any biocompatible gas may be entrapped in the microbubbles including air, nitrogen, halogenated hydrocarbon, including perfluorobutane, etc. (column 5, lines 10-67). Contrast agents comprising microbubbles of a perfluoroalkane such as perfluorobutane stabilized by phosphatidylserine are surprisingly stable (column 6, lines 1-12). Microbubbles have an average size of 0.1-10 micron (e.g. 1-7 micron). Contrast agents have a very narrow size distribution (column 6, lines 62+). Since preparation of the contrast agents typically involves a freeze-drying step, it may be advantageous to include a lyoprotective agent such as glycerol, a carbohydrate (e.g. sucrose, mannitol, etc.) or a polyglycol such as polyethylene glycol (column 7, lines 30-45). Contrast agents according to the invention may be prepared by generating a gas microbubble dispersion in an appropriate phospholipid containing aqueous medium and thereafter subjecting the dispersion to lyophilization to yield a dried reconstitutable product (column 7, lines 60+). The process for preparation of the contrast agents includes the following steps i) generating a dispersion of gas microbubbes in an aqueous medium containing a membrane-forming lipid; ii) lyophilizing the thus-obtained lipid-stabilized gas dispersion to yield a dried lipid-containing product and iii) reconstituting said dried product in an injectable liquid carrier. Step (i) may be effected by subjecting the liquid containing aqueous medium to an emulsion generating technique (e.g. sonication, etc) in the presence of a selected gas.

The aqueous medium may further contain enhancers or solubility aids for the lipid such as lipids or alcohols. The gas employed in the emulsification step need not be that desired in the final product. Thus most of this gas may be removed during the subsequent lyophilization step. Emulsification in the presence of a fluorinated alkane such as 4 or 5 carbon atoms may be particularly advantageous in terms of ultimately yielding end products with consistent and narrow size distribution. Emulsification may be done a room temperature or with heating (column 8, line 45 - column 9, line 40). A washing step may be performed (column 9, lines 49-55), as well as size-fractionation (column 10, lines 1-7).

It would have been obvious to one ordinary skill in the art at the time of the invention to modify the ratio of phospholipid / poloxamer in the lyophilisates disclosed by Linder, such as to provide greater amphiphilic material comprising greater than 50% by weight phospholipid as a matter of routine experimentation in preparation of reconstitutable composition for producing microbubble contrast agents. One would have been motivated to do so, and would have had a reasonable expectation of success in doing so because Unger and Dugstad teaches preparation of phospholipid vesicles comprising varying surfactant ratios, including those comprising predominantly phospholipid membranes. Furthermore the claims differ from the reference by reciting various concentrations of the active ingredient(s). However, the preparation of various pharmaceutical compositions having various amounts of the active agent is within the level of skill of one having ordinary skill in the art at the time of the invention. It has also been held that the mere selection of proportions and ranges is not patentable absent a

showing of criticality. See *In re Russell*, 439 F.2d 1228 169 USPQ 426 (CCPA 1971). With these things in mind a skilled artisan would have been motivated to combine the teaching of Linder teaching mixture of poloxamer with phospholipid with the teaching of Unger and Dugstad in order to provide a stable lyophilisate which is reconstitutable in aqueous system for preparing microbubble contrast agent. It would have been obvious to a skilled artisan to combine these teachings with an expected result of a stable composition comprising phospholipid and poloxamer capable of producing microbubble contrast agents. Furthermore, differences in concentration or temperature will generally not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." See *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); *In re Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382; or *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969).

With regard to claim 45, petroleum ether comprises pentane. With regard to claim 56 and 57, it is well-known in the art to wash or filter emulsions, as shown by Dugstad. With regard to claims 59-65, Linder discloses heating solutions at 50-60 C (and teaches nonpolar liquid with boiling point of 65); Dugstad teaches emulsions can be prepared at room temperature or with heating. With regard to claim 61, Unger teaches PEG-modified phospholipids are well known in the art of microbubbles. With regard to claim 69, Dugstad teaches that perfluorobutane as common biocompatible gas in microbubbles.

Conclusion

No claims are allowed at this time.

Although Applicant's arguments as set forth in the aforementioned Response have been fully considered, they are deemed unpersuasive. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is (571)272-9928. The examiner can normally be reached on Monday-Tuesday and Thursday-Friday 9 AM-5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

LHS